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Tenofovir in second-line ART in Zambia and South Africa: Collaborative analysis of cohort studies

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Abstract

Objectives—Tenofovir (TDF) is increasingly used in second-line antiretroviral treatment (ART) in sub-Saharan Africa. We compared outcomes of second-line ART containing and not containing TDF in cohort studies from Zambia and the Republic of South Africa (RSA).

Methods—Patients aged ≥ 16 years starting protease inhibitor-based second-line ART in Zambia (1 cohort) and RSA (5 cohorts) were included. We compared mortality, immunological failure (all cohorts) and virological failure (RSA only) between patients receiving and not receiving TDF. Competing risk models and Cox models adjusted for age, sex, CD4 count, time on first-line ART and calendar year were used to analyse mortality and treatment failure, respectively. Hazard ratios (HRs) were combined in fixed-effects meta-analysis.

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Author contributions

G.W, O.K. and M.E. designed the study. G.W. and O.K. performed the statistical analyses. G.W. and M.E. wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and to the final version of the manuscript. G.W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Findings—1,687 patients from Zambia and 1,556 patients from RSA, including 1,350 (80.0%) and 206 (13.2%) patients starting TDF, were followed over 4,471 person-years. Patients on TDF were more likely to have started second-line ART in recent years, and had slightly higher baseline CD4 counts than patients not on TDF. Overall 127 patients died, 532 were lost to follow-up and 240 patients developed immunological failure. In RSA 94 patients had virologic failure. Combined HRs comparing tenofovir with other regimens were 0.60 (95% CI 0.41–0.87) for immunologic failure and 0.63 (0.38–1.05) for mortality. The HR for virologic failure in RSA was 0.28 (0.09–0.90).

Conclusions—In this observational study patients on TDF-containing second-line ART were less likely to develop treatment failure than patients on other regimens. TDF seems to be an effective component of second-line ART in southern Africa.

Keywords

Tenofovir; second-line antiretroviral therapy; southern Africa; treatment failure; mortality

INTRODUCTION

Despite the unprecedented scale-up of antiretroviral treatment (ART) in resource-constrained settings, the proportion of patients switching to second-line ART after failing a first-line regimen is low in many resource-limited countries. Earlier detection of treatment failure and switching to second-line protease-inhibitor (PI)-based ART probably reduces mortality [2], but second-line regimens remain considerably more expensive than first line regimens. Only few studies have described clinical outcomes of patients on second-line therapy in sub-Saharan Africa [3–6].

As genotypic drug-resistance testing is not routinely available in the region, the World Health Organization (WHO) recommends the use of standardized second-line ART consisting of a ritonavir-boosted PI plus two nucleoside reverse transcriptase inhibitors (NRTIs). The NRTI backbone should include at least one new agent. Tenofovir (TDF) is increasingly used as a component of second-line ART in patients not previously exposed to this drug. In southern Africa TDF has only recently been introduced for use in first-line ART and the majority of patients failing their first-line regimen are therefore eligible to receive this drug in second-line ART. Although studies from Europe and North America showed favorable clinical outcomes in patients treated with TDF-containing salvage ART[8,9], outcomes of second-line regimens containing and not containing TDF have not been compared so far in southern Africa.

HIV-1 subtype C variant represents approximately 50% of global HIV infections and is most prevalent in southern Africa. The K65R mutation, which is associated with TDF resistance, is more frequent in HIV-1 subtype C compared to subtype B viruses, especially when suboptimal first-line regimens including stavudine (D4T) or didanosine (ddI) are used [10–12]. A study from Malawi showed that 23% of patients failing first-line ART developed the K65R mutation even without prior exposure to TDF [11]. In South Africa, where routine viral load monitoring shortens the time patients spend on failing first-line regimens, the proportion of patients with this mutation was much lower [13–15]. In Malawi clinical outcomes after one year were not affected by resistance [6].

We compared outcomes in patients receiving TDF-containing second-line ART with those on other second-line regimens in a collaborative analysis of six cohorts in Zambia and the Republic South Africa (RSA).

METHODS

Antiretroviral treatment programmes

The International epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) are a regional collaboration of ART programmes [16]. Data are collected at ART initiation (baseline) and each follow-up visit, using standardized instruments, and transferred to data centres at the Universities of Cape Town, Republic of South Africa (RSA) and Bern, Switzerland. All sites have ethical approval to collect data and to participate in IeDEA-SA.

We included all cohorts with more than 50 patients on second-line ART, and 10 or more patients on TDF and not on TDF. Six cohorts met inclusion criteria: the Centre for Infectious Disease Research in Zambia (MoH-CIDRZ) programme in Lusaka, Zambia and five cohorts from RSA: Aurum Institute (community and workplace ART program) and Themba Lethu clinic in Johannesburg, and the Khayelitsha and Tygerberg ART programs in Cape Town. In RSA viral load and CD4 cell counts are monitored every 6 months during the first year of ART and then yearly. In Zambia CD4 counts are monitored every 6 months but viral load measurements are not routinely performed. All treatment programmes trace patients lost to follow-up.

Eligibility criteria

All patients aged 16 years and older who started a second-line ART regimen were included. We defined second-line regimens according to the most recent WHO treatment guidelines as a boosted PI-based regimen, which followed a first-line regimen of one NNRTI and two NRTIs. At least one component of the NRTI backbone had to be replaced by a drug characterised by different resistance mutations pathways. For example, a change from lamivudine (3TC)/D4T to 3TC/zidovudine (AZT) was not considered an eligible backbone change. Patients with ineligible backbone changes and patients treated with a TDF-containing first-line regimen were excluded. The selection of study participants in Zambia and the Republic of South Africa are shown in Webfigures 1 and 2.

Outcomes

We examined time to immunological failure, time to virological failure and time to death, defining treatment failure as proposed by WHO. Briefly, there are 3 possible criteria for immunological failure: (i) a fall of CD4 count to baseline or below, (ii) a 50% fall from on-treatment peak value and (iii) persistent CD4 count levels below 100 cells/μl. Patients were considered to experience immunological failure if at least one of the 3 criteria were fulfilled on two consecutive CD4 cell measurements within 1 year. Virological failure, defined as 2 consecutive viral load measurements above 5,000 copies/ml within a year, was assessed in the South African cohorts.

Statistical analyses

Characteristics at the start of second-line ART were compared between patients on second-line regimens containing and not containing TDF using chi-squared and Mann-Whitney tests. We compared rates of immunological failure and virological failure in Cox regression models, measuring time from 6 months after switching to second-line ART. We used competing risk cumulative incidence curves [17] and competing risk regression models according to Fine and Gray [18] to compare mortality, measuring time from switching to second-line ART. Standard Kaplan-Meier curves ignore the competing risks of death and LTFU and may produce biased results[19]. All regression models included the variables gender, age (16–29, 30–39 or 40 years and over), CD4 cell count (0–49, 50–99, 100–199, over 200 cells/μl or "not measured") at the start of second-line ART, time on first-line

before switching to second-line ART (less than 18, 18–36 or over 36 months) and calendar year of starting second-line ART (before 2007, 2007, 2008, 2009 and 2010).

All analyses were done separately for Zambia and RSA. Sub-distribution hazard ratios (sHR) and hazard ratios (HR) were then combined in (inverse variance weighted) fixed-effects meta-analysis and shown in a stratified forest plot. Finally, in order to assess the effect of the first-line backbone on second-line outcomes, we examined whether the use of D4T in the first-line ART regimen predicted immunological failure in patients on TDF-containing second-line regimen. All statistical analyses were performed using Stata software version 11 (College Station, Texas, USA).

RESULTS

ART programmes and patients characteristics

Table 1 shows the composition of cohorts. A total of 3,243 patients on second-line ART, including 1,556 (48.0%) on a TDF-containing regimen were included in the analyses. The majority of patients were female in all cohorts except the workplace cohort in South Africa, which was dominated by male miners. The median age ranged from 32 years in Khayelitsha to 45 years in the Aurum workplace cohort. In Zambia, 80% of patients were on TDF-based second-line ART whereas in RSA this percentage ranged from 4% to 25%. Crude mortality rates were similar across South African cohorts except for the Aurum community cohort for which mortality was considerably lower, probably due to under ascertainment of deaths. Such under ascertainment may also explain the lower mortality in Zambia compared to RSA.

Both in Zambia and RSA, the proportion of patients on a TDF containing second-line regimen increased over the years, with the exception of a slight decrease in Zambia in 2010 (Table 2). The median age at start of second-line ART was higher in patients on TDF in Zambia, but identical in both treatment groups in RSA. Conversely, the sex distribution was similar in Zambia whereas in RSA, women were more likely to start a TDF containing regimen than men. In both countries, patients receiving TDF-containing regimens had higher CD4 cell counts and had spent more time on their first-line regimen before switching to second-line ART than those on other regimens. Most patients (3,225 patients; 99.4%) were treated with second-line regimens containing ritonavir-boosted lopinavir (LPV/r) and 1,468 (87.0%) of the patients not on a TDF-containing second-line regimen had a backbone of DDI/AZT or DDI/ABC.

Descriptive analyses of treatment failure, mortality and LTFU

Analyses of immunological treatment failure were based on 2,330 patients (71.8% of total study population) with at least six months of follow-up after starting second-line ART. Virological failure was examined in 992 patients (63.8% of patients treated in RSA). Over 2,782 person-years, 94 patients (7.9%) on TDF and 146 patients (12.8%) on other second-line regimens developed immunological failure. The crude incidence rate of immunological failure was 69.9 (95% CI 57.1–85.6) per 1,000 person-years in the TDF group and 101.6 (86.4–119.4) per 1,000 person-years in the other group. In South Africa, three patients (2.7%) in the TDF group and 107 patients (12.1%) in the group without TDF experienced virological failure. Figure 1 shows the Kaplan-Meier curves of immunological failure in Zambia and virological failure in South Africa, by treatment group.

Over 4,471 person-years, 127 patients (3.9%) died and 532 (16.4%) were LTFU (Table 1). Crude rates per 1000 person-years ranged from 6.5 (95% CI 1.6–25.9) to 45.2 (27.3–75.0) for mortality and from 54.6 (34.4–86.7) to 165.8 (127.3–216.0) for LTFU. Figure 2 shows the cumulative incidence of mortality and LTFU by country and type of second-line ART

from the competing risk analysis. At 3 years, 3.3% of patients (95% CI 2.3–4.5%) in the TDF group in Zambia and 4.4% (95% CI 1.8–8.8) in South Africa were known to have died. These proportions were higher in the groups treated without TDF: 9.0% (95% CI 6.9–12.7%) in Zambia and 7.8% (95% CI 5.8–10.00) in South Africa. LTFU at 3 years was higher in Zambia than in RSA. In Zambia, LTFU was somewhat higher in patients on TDF compared to patients not on TDF whereas the opposite was observed in RSA: LTFU was lower in patients on TDF compared to other patients (Figure 2). These analyses were not adjusted for differences in patient characteristics at the start of second-line ART and therefore have to be interpreted with caution.

Regression analyses of treatment failure and mortality

Figure 3 presents the results from the Cox and competing risk regression analyses adjusted for age, sex, CD4 count, time on first-line ART and calendar year, and meta-analyses of these estimates. Results for immunological failure were closely similar in Zambia and RSA (p from test of heterogeneity 0.99), with a combined HR comparing TDF with other regimens of 0.60 (95% CI 0.41–0.87). Similarly, the hazard of virologic failure was reduced with TDF in RSA: HR 0.22 (95% CI 0.07–0.71). Mortality was lower in patients on a TDF-containing regimen compared to those on other regimens in Zambia but not in RSA. However, confidence intervals overlapped and the test of heterogeneity was not statistically significant (p=0.13). The combined subdistribution HR for mortality was 0.63 (95% CI 0.38–1.05).

Results for all variables included in the models are shown in webtable 1 for Zambia and webtable 2 for RSA. In both settings, male patients and those under 30 years of age were more likely to experience treatment failure. Time spent on first-line ART before switching to a second-line regimen did not affect outcomes. Finally, in patients on TDF-containing second-line regimens, the risk of second-line immunological failure in the TDF-group was slightly increased if D4T was used in the first-line backbone, however, confidence intervals around the HR (adjusted for all variables listed above) were wide and included both a decrease and increase of the risk of failure: HR 1.30 (95% CI 0.84–2.02).

DISCUSSION

Even though several countries in southern Africa have introduced TDF in first-line ART, most patients who will be failing their first-line regimen in the coming years will not have been exposed to TDF. As a consequence, these patients might benefit from this drug in their second-line regimen. The comparative effectiveness of second-line regimens including or excluding TDF in southern Africa is therefore of great interest. We compared clinical outcomes between patients receiving TDF-containing second-line ART and patients treated with other second-line regimens in six ART programmes in Zambia and RSA. Overall, mortality and the rate of treatment failure were low in this population, underlining the benefit of PI-based second-line ART in patients failing first-line treatment in the region[20]. In Zambia, LTFU was similar in patients on second-line ART containing and not containing TDF, but mortality and immunological failure were lower in patients on TDF. In the five South African cohorts with access to routine viral load monitoring the rate of virological failure was also lower in the TDF group.

In contrast to Zambia the use of TDF was not associated with reduced mortality in South Africa. This finding could be the result of differences in the capacity of the health system in South Africa compared to Zambia or reflect differences in ascertainment of deaths and tracing of patients LTFU. Confounding by indication could be another explanation: the relatively few patients who were prescribed TDF in South Africa before 2010 might have been a selected group of sicker patients. Finally, the difference between the two countries

could reflect the play of chance: the confidence intervals overlapped widely and a formal test of heterogeneity gave a p value of 0.13. We can thus not exclude a similar reduction in mortality in RSA.

In both groups mortality after one year of second-line ART was somewhat lower than the 5.4% mortality observed after a median of 15.1 months in the Médecins sans Frontiéres (MSF) multi-cohort study of patients on second-line ART [3]. In contrast, in a study of patients virologically failing first-line ART in Malawi, 10% of patients on second-line ART died during the first six months [6]. The higher mortality in the latter study might be explained by the presence of virological failure in all patients and the very low median CD4 count at the start of second-line ART. Furthermore, patients who are treated in settings without access to routine viral load monitoring are at risk of remaining on failing first-line regimens for long periods before switching to second-line ART[2,21], and of accumulating drug resistance mutations which might limit the efficacy of some second line regimens[11].

Studies from different regions in sub-Saharan Africa showed a high prevalence of TDF-related resistance mutations in patients failing first-line ART [10,11,22]. This raised concerns on the efficacy of TDF in second-line regimens for populations infected with subtype C HIV-1 variants. In high-income countries, the K65R mutation is present only in 2–5% of HIV-1 subtype B infected patients failing first-line ART [23]. In contrast, over 20% of patients failing first-line ART in an urban public-sector ART clinic in Malawi had developed this resistance mutation, without prior exposure to TDF [11]. Interestingly, in the Malawian study, and the PharmAccess African Studies to Evaluate Resistance (PASER), clinical outcomes one year after initiation of second-line ART were not affected by resistance to TDF [6,24]. Another report from PASER nevertheless argued that in light of the high prevalence of the K65R mutation in patients failing a D4T-containing regimen, AZT might be a better option for second-line ART than TDF[12]. Prolonged treatment with a failing D4T-containing first-line regimen might explain the high levels of TDF resistance mutations in the region [23]. We found little evidence for an association of the risk of second-line treatment failure with the presence of D4T in the first-line regimen, however, the power of our study to detect smaller effects was limited.

There are several possible explanations for the superior effect of TDF in second-line ART in Zambia and South Africa. More than 80% of the patients not on TDF were treated with either DDI/AZT or DDI/ABC as the NRTI backbone. Due to its better tolerability and once-daily dosing, treatment adherence might be higher in patients receiving TDF compared to other NRTI combinations, especially those including DDI: the higher toxicity of DDI-based regimens might have led to poorer adherence. Wallis et al. and Van Zyl et al. reported a low prevalence of PI mutations in patients failing second-line ART in the Republic of South Africa [25,26], indicating that failure was due to insufficient drug levels following non-adherence, rather than resistance. Finally, the high potency of LPV/r monotherapy in patients without prior PI exposure could have masked larger differences in treatment outcomes between the two groups [27,28]. Patients on TDF-containing second-line regimens might have had favourable outcomes despite potential NRTI mutations, including thymidine-analogue mutations (TAM's) and K65R. Of note, the difference in treatment failure between the two second-line regimens emerged already after one year in RSA, whereas it was only apparent later during follow-up in Zambia. This could be explained by the earlier diagnosis of treatment failure with virological monitoring in RSA compared to CD4 monitoring in Zambia.

To our knowledge this is the first study to compare second-line regimens in southern Africa. In particular, there are no randomized trials of second-line ART tailored to regions where non-B HIV subtypes dominate. The main limitation of multi-cohort data comparing

treatments lies in the lack of randomization and the heterogeneity between the different treatment sites. Confounding by indication and differences between settings in background mortality, monitoring and treatment strategies, and health systems may have biased our results. Of note, the proportion of patients on a TDF-containing second-line regimen varied widely across countries and calendar time, reflecting national treatment guidelines. However, the association of TDF with reduced rates of treatment failure was consistent within countries and cohorts, which adds strength to our findings. Furthermore, over 99% of the patients received the same PI, thus effectively removing one potential source of confounding. We had no data on treatment adherence, which is known to influence ART outcomes[29–31]. Young age and male gender were risk factors for second-line failure, probably as a consequence of the lower adherence to ART in younger patients and men [32,33]. Finally, as no genotypic resistance data is routinely collected in southern Africa, we could not assess the relationship between treatment failure, resistance patterns and clinical outcomes.

We did not evaluate toxicity and side-effects related to the different regimen. Most patients on non-TDF second-line ART had DDI in their backbone. The toxicities of DDI, including lipodystrophy, gastrointestinal intolerance, peripheral neuropathy and pancreatitis, will have influenced our results.[34,35] TDF is associated with nephrotoxicity, including an increased risk of loss of kidney function, acute renal failure and tubulopathy[36,37]. A recent study from South Africa showed that pre-existing renal disease was frequently exacerbated by the use of tenofovir[38]. Furthermore, patients on PI-based regimens may be at increased risk of renal failure[39]. Screening for renal dysfunction before the initiation of TDF-containing regimen and close monitoring during treatment is part of treatment guidelines and should be performed routinely.

In conclusion, we found that patients on TDF-containing second-line ART were less likely to develop treatment failure in all cohorts and less likely to die in Zambia than patients on other regimens. Despite the increased prevalence of TDF-related resistance mutations in patients failing first-line ART in southern Africa, TDF seems to be an effective component of second-line ART for many patients who have not been exposed to this drug previously. This finding is of considerable importance, as an increasing number of TDF-unexposed patients failing their first-line treatment will be switched to TDF-containing second-line regimen in the coming years. Second-line ART is becoming more available in sub-Saharan Africa, but most ART programmes in the region do not have access to individual genotypic resistance data. Thus, randomized trials comparing the efficacy and toxicities of different second-line regimens are urgently needed to inform clinical practice and guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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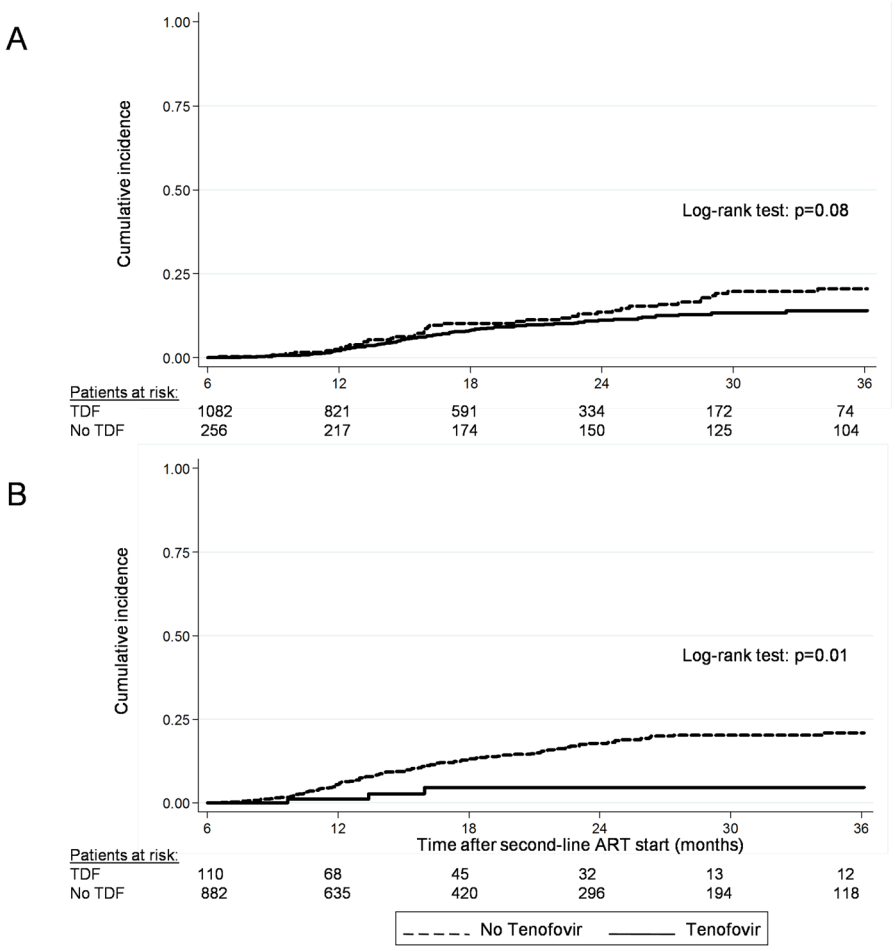

FIGURE 1.

Cumulative incidence of immunological failure in Zambia (A) and virological failure in the Republic of South Africa (B) during the first three years of second-line ART. TDF, tenofovir.

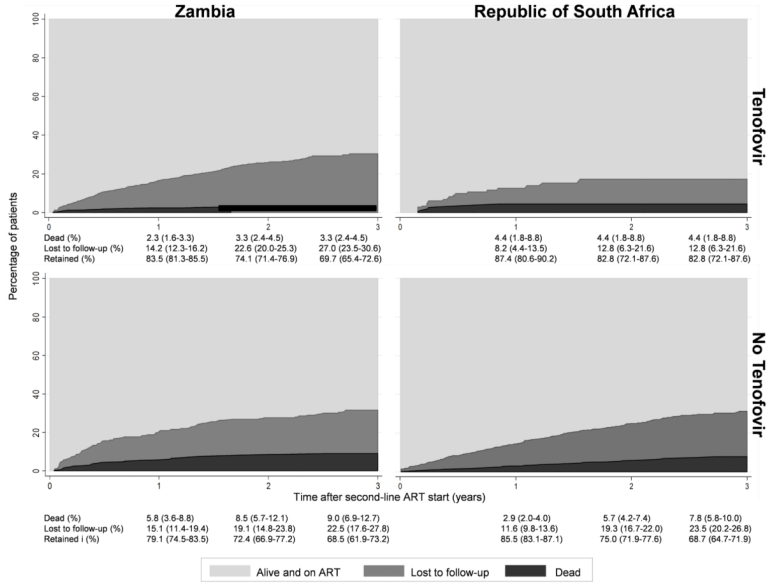

FIGURE 2.
Retention in care by second-line ART category and country.

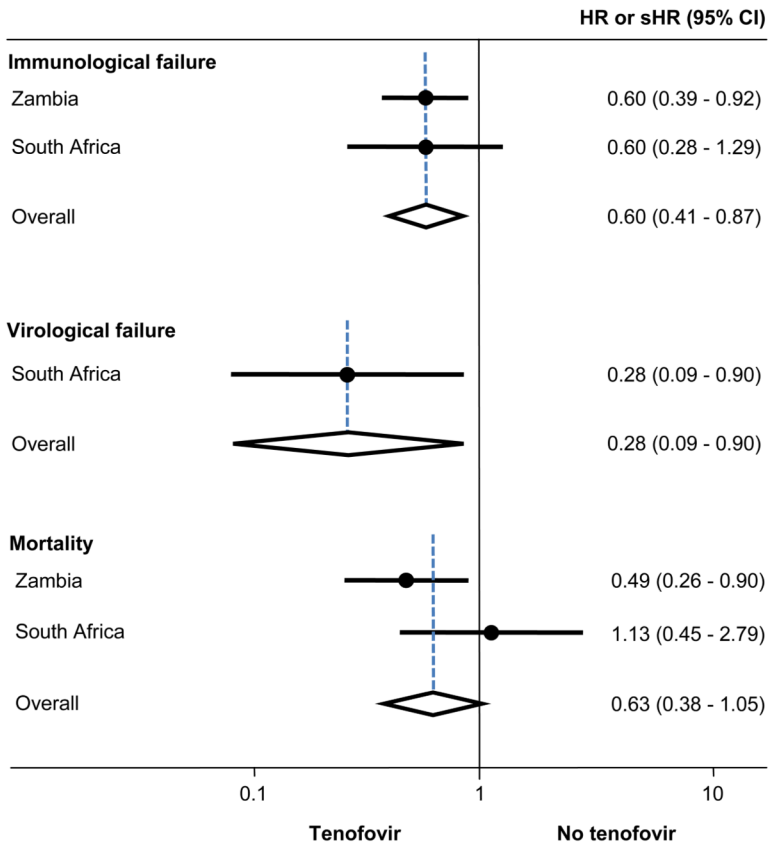

FIGURE 3.

The risk of treatment failure and death on secondline ART containing and not containing tenofovir in Zambia and the Republic of South Africa. The estimates shown are hazard ratios (HR) for immunological and virological failure and subdistribution hazard ratios (sHR) for mortality.

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Table 1

Characteristics of participating antiretroviral therapy (ART) programmes.

Sites	No. of patients	Female (%)	Median age in years (IQR)	No. on second-line ART with TDF (%)	Viral load monitoring	Follow-up time on second-line ART (py)	Mortality (95% CI) (per 1,000 py)	LTFU (95% CI) (per 1,000 py)
South Africa								
Aurum-C	323	209 (65)	38 (32–44)	80 (25)	Yes	309	6.5 (1.6–25.9)	145.7 (108.8–195.1)
Aurum-W	262	15 (6)	45 (38–51)	10 (4)	Yes	331	45.2 (27.3–75.0)	165.8 (127.3–216.0)
Khayelitsha	197	144 (73)	32 (28–40)	13 (7)	Yes	227	30.8 (14.7–64.7)	61.7 (36.5–104.1)
Themba Lethu	562	341 (61)	36 (32–43)	81 (14)	Yes	766	35.3 (24.2–51.4)	105.8 (85.1–131.5)
Tygerberg	212	139 (66)	35 (31–42)	22 (10)	Yes	329	39.5 (22.9–68.0)	54.6 (34.4–86.7)
Zambia								
CIDRZ	1,687	954 (57)	38 (33–45)	1,350 (80)	No	2,508	25.1 (19.6–32.2)	127.2 (114.0–141.9)
Total	3,243	1,802 (55.6)	38 (32–45)	1,556 (48.0)		4,471	28.4 (23.9–33.8)	119.0 (109.3–129.5)

Py, person-years; LTFU, loss to follow-up; Aurum-C, Aurum Community cohort; Aurum-W, Aurum workplace cohort.

Table 2

Patient characteristics at start of second-line antiretroviral therapy

		Zambia			South Africa		
	All patients (N=3,243)	**Tenofovir (N=1,350)**	**No Tenofovir (N=337)**	**P**	**Tenofovir (N=206)**	**No Tenofovir (N=1,350)**	**P**
Female gender (%)	1,802 (55.6)	757 (56.1)	197 (58.5)	0.43	137 (66.5)	711 (52.7)	<0.001
Median age at start (IQR)	38 (32–45)	39 (33–45)	37 (32–43)	0.003	37 (32–43)	38 (32–45)	0.37
Median CD4 count at start (IQR)	172 (95–267)	161 (92–261)	135 (77–242)	0.05	206 (97–339)	185 (103–270)	0.05
missing (%)	349 (10.8)	183 (13.6)	46 (13.6)		23 (11.1)	97 (7.2)	
Median time on first-line ART in months (IQR)	27 (17–38)	33 (23–43)	27 (18–35)	<0.001	24 (15–34)	22 (14–32)	0.04
Calendar year of second-line ART start (%)				<0.001			<0.001
Before 2007	405 (12.5)	5 (0.4)	53 (15.7)		22 (10.7)	325 (24.1)	
2007	695 (21.4)	164 (12.2)	122 (36.2)		32 (15.5)	377 (27.9)	
2008	909 (28.0)	445 (33.0)	57 (16.9)		44 (21.4)	363 (26.9)	
2009	889 (27.4)	487 (36.1)	59 (17.5)		86 (41.8)	257 (19.0)	
2010	345 (10.6)	249 (18.4)	46 (13.7)		22 (10.7)	28 (2.1)	
Most common second-line ART backbone (%)	FTC/TDF (37.5)	FTC/TDF (85.8)	DDI/ABC (79.8)		TDF/FTC (28.4)	DDI/AZT (71.1)	
	DDI/AZT (29.8)	3TC/TDF (8.0)	ABC/3TC (16.6)		3TC/TDF (26.9)	DDI/ABC (17.5)	
	DDI/ABC (15.6)	FTC/AZT/TDF (5.9)	DDI/3TC (1.2)		AZT/3TC/TDF (12.2)	DDI/D4T (2.4)	

Categorical variables are compared with chi-squared, continuous variables with Mann-Whitney tests. Viral load is routinely monitored in South Africa only. IQR; interquartile range. FTC: emtricitabine; TDF: tenofovir; DDI: didanosine; AZT: zidovudine; ABC: abacavir; 3TC: lamivudine